



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-N-0231]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Adverse Experience Reporting for Licensed Biological Products; and General Records

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or we) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202-395-7285, or emailed to oir_submission@omb.eop.gov. All comments should be identified with the OMB control number 0910-0308. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Ila S. Mizrachi, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-7726, PRASStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Adverse Experience Reporting For Licensed Biological Products; and General Records--

21 CFR Part 600

OMB Control Number 0910-0308--Extension

Under the Public Health Service Act (42 U.S.C. 262), FDA may only approve a biologics license application for a biological product that is safe, pure, and potent. When a biological product is approved and enters the market, the product is introduced to a larger patient population in settings different from clinical trials. New information generated during the postmarketing period offers further insight into the benefits and risks of the product, and evaluation of this information is important to ensure its safe use. FDA issued the Adverse Experience Reporting (AER) requirements in part 600 (21 CFR part 600) to enable FDA to take actions necessary for the protection of the public health in response to reports of adverse experiences related to licensed biological products. The primary purpose of FDA's AERS is to identify potentially serious safety problems with licensed biological products. Although premarket testing discloses a general safety profile of a biological product's comparatively common adverse effects, the larger and more diverse patient populations exposed to the licensed biological product provides the opportunity to collect information on rare, latent, and long-term effects. In addition, production and/or distribution problems have contaminated biological products in the past. AER reports are obtained from a variety of sources, including manufacturers, patients, physicians, foreign regulatory agencies, and clinical investigators. Identification of new and unexpected safety issues through the analysis of the data in AERS contributes directly to increased public health protection. For example, evaluation of these

safety issues enables FDA to take focused regulatory action. Such action may include, but is not limited to, important changes to the product's labeling (such as adding a new warning), coordination with manufacturers to ensure adequate corrective action is taken, and removal of a biological product from the market when necessary.

Section 600.80(c)(1) requires licensed manufacturers or any person whose name appears on the label of a licensed biological product to report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the licensed manufacturer. These reports are known as postmarketing 15-day Alert reports. This section also requires licensed manufacturers to submit any followup reports within 15 calendar days of receipt of new information or as requested by FDA, and if additional information is not obtainable, to maintain records of the unsuccessful steps taken to seek additional information. In addition, this section requires that a person who submits an adverse action report to the licensed manufacturer rather than to FDA, maintain a record of this action. Section 600.80(e) requires licensed manufacturers to submit a 15-day Alert report for an adverse experience obtained from a postmarketing clinical study only if the licensed manufacturer concludes that there is a reasonable possibility that the product caused the adverse experience. Section 600.80(c)(2) requires licensed manufacturers to report each adverse experience not reported in a postmarketing 15-day Alert report at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals. The majority of these periodic reports are submitted annually, since a large percentage of currently licensed biological products have been licensed longer than 3 years. Section 600.80(k) requires licensed manufacturers to maintain for a period of 10 years records of all adverse experiences known to the licensed manufacturer, including raw data and any

correspondence relating to the adverse experiences. Section 600.81 requires licensed manufacturers to submit, at an interval of every 6 months, information about the quantity of the product distributed under the biologics license, including the quantity distributed to distributors. These distribution reports provide FDA with important information about products distributed under biologics licenses, including the quantity, certain lot numbers, labeled date of expiration, the fill lot numbers for the total number of dosage units of each strength or potency distributed (e.g., 50,000 per 10-milliliter vials), and date of release. FDA may require the licensed manufacturer to submit distribution reports under this section at times other than every 6 months. Under § 600.82(a), an applicant of a biological product or blood and blood component must notify FDA of a permanent discontinuance of manufacture or an interruption in manufacturing or disruption in supply, as applicable. Under §§ 600.80(h)(2) and 600.81(b)(2), a licensed manufacturer may request a temporary waiver for the requirements under § 600.80(h)(1) and (b)(1), respectively. Requests for waivers must be submitted in accordance with § 600.90. Under § 600.90, a licensed manufacturer may submit a waiver request for any requirements that apply to the licensed manufacturer under §§ 600.80 and 600.81. A waiver request submitted under § 600.90 must include supporting documentation.

Manufacturers of biological products for human use must keep records of each step in the manufacture and distribution of a product, including any recalls. These recordkeeping requirements serve preventative and remedial purposes by establishing accountability and traceability in the manufacture and distribution of products. These requirements also enable FDA to perform meaningful inspections. Section 600.12 requires, among other things, that records be made concurrently with the performance of each step in the manufacture and distribution of products. These records must be retained for no less than 5 years after the records

of manufacture have been completed or 6 months after the latest expiration date for the individual product, whichever represents a later date. In addition, under § 600.12, manufacturers must maintain records relating to the sterilization of equipment and supplies, animal necropsy records, and records in cases of divided manufacturing responsibility with respect to a product. Under § 600.12(b)(2), manufacturers are also required to maintain complete records pertaining to the recall from distribution of any product. Furthermore, § 610.18(b) (21 CFR 610.18(b)) requires, in part, that the results of all periodic tests for verification of cultures and determination of freedom from extraneous organisms be recorded and retained. The recordkeeping requirements for §§ 610.12(g), 610.13(a)(2), 610.18(d), 21 CFR 680.2(f), and 680.3(f) are approved under OMB control number 0910-0139.

Respondents to this collection of information include manufacturers of biological products (including blood and blood components) and any person whose name appears on the label of a licensed biological product. In table 1, the number of respondents is based on the estimated number of manufacturers that are subject to those regulations or that submitted the required information to the Center for Biologics Evaluation and Research and Center for Drugs Evaluation and Research, FDA, in fiscal year (FY) 2016. Based on information obtained from the FDA's database system, there were 93 manufacturers of biological products. This number excludes those manufacturers who produce Whole Blood, components of Whole Blood, or in-vitro diagnostic licensed products, because of the exemption under § 600.80(m). The total annual responses are based on the number of submissions received by FDA in FY 2016. There were an estimated 125,371 15-day Alert reports, 180,580 periodic reports, and 677 lot distribution reports submitted to FDA. The number of 15-day Alert reports for postmarketing studies under § 600.80(e) is included in the total number of 15-day Alert reports. FDA received

81 requests from 40 manufacturers for waivers under § 600.90 (including §§ 600.80(h)(2) and 600.81(b)(2)), of which 79 were granted. The hours per response are based on FDA experience. The burden hours required to complete the MedWatch Form (Form FDA 3500A) for § 600.80(c)(1), (e), and (f) are reported under OMB control number 0910-0291.

In the *Federal Register* of July 18, 2017 (82 FR 32836), FDA published a 60-day notice requesting public comment on the proposed collection of information. No comments were received.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden¹

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response (in hours)	Total Hours
600.80(c)(1), 600.80(d), and 600.80(e); postmarketing 15-day Alert reports	93	1,348.07	125,371	1	125,371
600.82; notification of discontinuance or interruption in manufacturing	18	1.61	29	2	58
600.80(c)(2); periodic adverse experience reports	93	1,941.72	180,580	28	5,056,240
600.81 Distribution Reports	93	7.28	677	1	677
600.80(h)(2), 600.81(b)(2), and 600.90; waiver requests	40	2.03	81	1	81
Total					5,182,427

¹There are no capital costs or operating and maintenance costs associated with this collection information.

In table 2 the number of respondents is based on the number of manufacturers subject to those regulations. Based on information obtained from FDA's database system, there were 263 licensed manufacturers of biological products in FY 2016. However, the number of recordkeepers listed for § 600.12(a) through (e) excluding (b)(2) is estimated to be 114. This number excludes manufacturers of blood and blood components because their burden hours for recordkeeping have been reported under § 606.160 in OMB control number 0910-0116. The total annual records is based on the annual average of lots released in FY 2016 (7,198), number of

recalls made (575), and total number of adverse experience reports received (305,951) in FY 2016. The hours per record are based on FDA experience.

FDA estimates the burden of this recordkeeping as follows:

Table 2.--Estimated Annual Recordkeeping Burden¹

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeper (in hours)	Total Hours
600.12 ² ; maintenance of records	114	63.14	7,198	32	230,336
600.12(b)(2); recall records	263	2.19	575	24	13,800
600.80(c)(1) and 600.80(k)	93	3,289.79	305,951	1	305,951
Total					550,087

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

²The recordkeeping requirements in § 610.18(b) are included in the estimate for § 600.12.

The burden for this information collection has changed since the last OMB approval.

Because of an increase in the number of AER reports we have received during the past 3years, we have increased our reporting and recordkeeping burden estimates.

Dated: January 2, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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